



**Bristol-Myers Squibb Company**

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**Dockets Management Branch  
Food and Drug Administration, HFA-305  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852**

**Re: Docket No. 2005D-0183; Proposed Draft Guidance, *Guidance for Industry: Antiviral Drug Development — Conducting Virology Studies and Submitting Data to the Agency, Federal Register Vol. 70, No. 100, pp. 30127 - 30128 (May 25, 2005)***

Dear Sir or Madam:

Bristol-Myers Squibb (BMS) is a worldwide healthcare company, and our mission is to extend and enhance human life by providing the highest-quality pharmaceutical and related healthcare products. Among the medicines that we develop and distribute are those for the treatment of HIV and hepatitis B (HBV) and C (HCV) viruses. For this reason, we are pleased to have the opportunity to offer comments on the Draft Guidance.

**1. Summary of BMS Comments on Proposal**

We commend the FDA's efforts to clarify the regulatory expectations and provide a consistent approach to antiviral drug development for HIV, HBV, and HCV. The Draft Guidance provides an overall structure for the nonclinical virology reports and resistance data templates. Our comments on specific aspects of the Draft Guidance are set forth below. There are a few aspects of the guidance that appear to warrant clarification, and we will note apparent inconsistencies as appropriate.

**2. Specific Comments**

**A. Nonclinical Virology Reports: Recommended Components of Nonclinical Virology Reports**

**In Vitro Combination Activity Analysis, page 7, line 283**

The guidance recommends that sponsors evaluate in vitro antiviral activity of investigational drugs in two- or three-drug combinations with other drugs approved for the same indication. BMS would caution that the interpretation of in vitro antiviral activity assessments of three-drug combinations can be difficult.

**Resistance, page 8, lines 325 - 336**

The guidance provides two basic methods that can be employed to isolate viruses that have reduced susceptibility to the investigational drug. The optimized method is drug-specific; however, the use of the terms "first method" and "second method" implies that one method is preferred to the other. FDA may want to consider wording that offers more latitude to customize the method based on the target.

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## **B. Proposal for Monitoring Resistance Development**

### **Page 11, lines 465 - 467**

The guidance suggests collecting genotypic and phenotypic data for baseline isolates from all patients and endpoint isolates from all virologic failures and discontinuations. BMS agrees that it is optimal to collect baseline for all subjects and post-treatment isolates for subjects with virologic failure; however, it may be appropriate to assess only paired specimens for those subjects with virologic failure. FDA may want to consider wording that recommends the baseline and post-treatment assessment of isolates in studies as appropriate, depending on the clinical study protocol or population (i.e., naive, early failure, or multiple-treatment failure patients).

Additionally, the wording regarding “virologic failures and discontinuations” is not entirely consistent with the wording in Appendices 2 and 3, which states “when the subject is on study drug” (lines 686 and 798, respectively). It would be helpful to include clarification in this section that endpoint isolates from all virologic failures and discontinuations should be collected while the subject is still receiving study drug. It would also be helpful to include this clarification in Appendix 1 (Page 13, lines 529-530 and Page 15, lines 591 - 592), Appendix 2 (Page 20, lines 740 - 741), and Appendix 3 (Page 24, lines 853 - 854).

## **C. Appendix 1: Template for Submitting HIV Resistance Data**

### **Page 13, lines 532 - 539**

The definition of virologic failure provided is different than that for virologic failures provided on page 11 (lines 468 - 474) and appears to be for HBV, rather than HIV. Further, this definition is for virologic one log suppression (VOLS), a definition that may be appropriate in multiple-treatment failure patients, but may not be universally appropriate in all populations. BMS suggests the use of a consistent definition for virologic failure for HIV on pages 11 and 13.

### **Page 14, lines 572 - 574**

The guidance recommends including genotypic data for gp160 (for agents targeting entry only). BMS suggests that genotypic data be restricted to the target protein/substrate only, except in the case that phenotypic resistance is observed in the absence of mutations in the target protein. In that situation, BMS suggests other proteins should be genotyped to determine the genetic cause of the observed resistance.

### **Page 14, lines 576 - 577**

The guidance states that the example “does not include all column headings as ‘previously’ suggested”; however, the recommended column headings are not identified until a subsequent section. Wording to the effect of “does not include all column headings as subsequently identified” would be more appropriate.

## **D. Appendix 3: Template for Submitting HCV Resistance Data**

### **Page 22, lines 800 - 807**

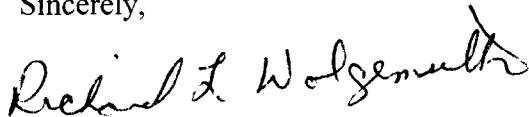
The definition of virologic failure provided appears to be for HBV. The definition should be corrected for HCV.

**Page 23, lines 834 - 835**

The guidance suggests that sponsors analyze HCV RNA with a sensitive and specific HCV RNA assay with lower limits of quantification in the range of less than 100 copies/mL. However, the Bayer VERSANT HCV RNA 3.0 (bDNA) Assay, which is routinely used, has a lower limit of detection of about 3,200 copies/mL. The more sensitive Bayer VERSANT HCV RNA Qualitative Assay has a lower limit of detection of approximately 300 copies/mL. Therefore, BMS would recommend that FDA consider using an HCV RNA assay threshold that is more in alignment with these standardly used assays.

BMS appreciates the opportunity to provide comments and respectfully requests that FDA give consideration to our recommendations. We would be pleased to provide additional input as requested.

Sincerely,

A handwritten signature in black ink, reading "Richard L. Wolgemuth". The signature is written in a cursive style with a large, stylized "R" and "W".

Richard L. Wolgemuth, Ph.D.  
Senior Vice President  
Global Regulatory Sciences